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EXAMINER
RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
1642	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/684,890	Applicant(s) Zentgraf et al
	Examiner Rawlings	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 18, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *12-28* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *12* is/are allowed.

6) ☒ Claim(s) *13-28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed April 18, 2002 (Paper No. 6) in response to the Office Action of December 18, 2001 (Paper No. 5) is acknowledged and has been entered. Previously pending claims 1-11 have been canceled, and new claims 13-28 have been added. Claims 12-28 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

3. Claims 13-28 are rejected under 35 USC 112, first paragraph essentially for the reasons previously set forth in Paper No. 5, Section 3, pages 2-6.

Applicant argues that (a) Nup88 may be potentially a significant marker given its dramatic overexpression in a broad spectrum of malignant tumors of literally all denominations and Table 1 lists more than fifty cancers that applicants tested for the overexpression of Nup88 and Applicant points to pages 10-11 of the specification, (b) given the teachings in the specification, the skilled artisan would know how to use an antibody that binds to Nup88 to determine the level of expression of that protein in a cell and that a level of expression of Nup88 in a test sample between 1.5 and 5 times greater than that of a normal control sample would indicate that the test sample contains cancerous cells. The argument has been considered but has not been found persuasive because (a') it is not clear that Nup88 is overexpressed in cancers other than breast carcinoma compared to normal control of the same tissue or cell type since no other normal controls appear to be disclosed. Further, a review of pages 10-11 reveal that negative controls were not "normal" samples, but rather

samples that were assayed in the absence of primary antiserum (see page 11) (b') although one would know how to determine the level of expression of that protein given the teaching in the specification, one would not know that a cancer cell was being identified for the reasons set forth previously and above.

New Matter

4. Claims 13-28 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "a sample comprising the protein bearing Accession number YO8612 at a level of expression that is between 1.5 and 5 times greater than normal, is indicative of a cancer cell" claimed in Claim 13 has no clear support in the specification and the claims as originally filed. In Paper No. 6, page 8, Applicant appears to suggest support for the newly claimed limitation wherein it is stated that "having read the specification, the skilled artisan would be apprised of the fact that if the level of expression of Nup88 in a test sample is at least between 1.5 and 5 times greater than that of a normal control sample, then that test sample contains cancer cells". The suggested support is not persuasive because a review of the specification revealed only a statement that densitometric quantification of the blots showed an increased expression in carcinomas between 1.5 and 5 times as compared with normal controls (p. 16, lines 17-18). A further review revealed that the increased expression is drawn only to breast cancer cells compared to normal control since no other normal controls of the same tissue type are recited. Thus, the newly added limitation is supported in the claims and specification only for breast cancer cells. There does not appear to be guidance for the cut-off range for any

other cancer type, the specification does not reveal that this particular range was contemplated for all cancer types at the time the invention was made. The subject matter claimed in claims 13-28 broadens the scope of the invention as originally disclosed in the specification.

5. Claim 22 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a chimeric protein which comprises at least one CDR region of the monoclonal antibody bearing accession number DSM ACC 2457 has no clear support in the specification and the claims as originally filed. A review of the specification reveals support for chimeric proteins wherein at least one CDR region of said monoclonal antibody is virtually identical with the corresponding counterpart of 149/1/1. However, in the absence of the limitation drawn to "virtually identical" the newly added limitation is not supported by the specification of claims as originally filed. The subject matter claimed in claim 22 broadens the scope of the invention as originally disclosed in the specification.

6. Claim 23 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a diagnostic kit for carrying out the method of claim 13 for determining the amount of protein binding molecule in a tissue biopsy sample has no clear support in the specification and the claims as originally filed. Applicant does not point to support in the specification and a review of the specification and claims did not reveal any support for the newly added limitation. The subject matter claimed in claim 23 broadens the scope of the invention as originally disclosed in the specification.

Enablement and Scope of Enablement

7. Claims 17 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of assaying the claimed protein with an antibody molecule, does not reasonably provide enablement for the claimed method with a protein binding molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method of diagnosing cancer by assaying a sample with a protein binding molecule. This includes any molecule that will bind to the protein consisting of the amino acid sequence of accession number YO8612. The specification teaches that protein binding molecules may be natural antibodies or recombinant antibodies such as chimeric proteins that exhibit homology to antibodies. One cannot extrapolate the teaching of the specification to the scope of the claims because no protein binding molecules other than antibody constructs are taught. The protein consisting of the amino acid sequence of accession number YO8612 is apparently a novel protein and thus the novel protein is an undeveloped art. There are no known ligands, no inhibitors, no cofactors to the apparently novel protein. The specification provides no guidance as to sources of other protein binding molecules. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict which "molecules", other than antibody constructs, would function as claimed with a reasonable expectation of success. For the above

reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. Claims 18 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of determining the level of expression of the protein consisting of the amino acid sequence of Accession number YO8612 comprising annealing a nucleic acid binding molecule to a nucleic acid transcript encoding said protein. This includes a whole universe of nucleic acid transcripts since the degeneracy of the code is notoriously well known in the art. The specification teaches that it is well known in the art that overexpression of proteins is usually accompanied by the up-regulation of the production of the corresponding transcripts, thus overexpression of the protein can be shown indirectly by measuring the amount of the corresponding transcripts. This can be done by the use of nucleic acid binding molecules to bind the transcript and nucleic acid binding molecules include DNA heteromers or RNA heteromers (p. 6). One cannot extrapolate the teaching of the specification to the scope of the claims because the specification provides neither guidance on nor exemplification of either nucleic acid binding molecules that will distinguish the claimed nucleic acid transcript in order to determine whether the transcript is up-regulated or annealing/hybridization conditions required so that the invention will function as claimed. Because of the well known degeneracy of the genetic code the nucleic acid sequence of the

encoding transcript could be represented by an almost unlimited number of variants. It cannot be determined which sequence(s) of the encoding transcript would be useful for distinguishing said transcript for the invention to function as claimed, that is, which sequences would be unique to any particular transcript that encodes the claimed amino acid sequence. Further, it is notoriously well known in the art that annealing conditions vary broadly from low to high stringency and that the ability of a particular probe to distinguish a particular transcript is dependent upon the critical conditions used. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

9. If Applicant were able to overcome the rejections above, Claims 18 and 24 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining protein expression comprising binding a protein-binding molecule to a protein, does not reasonably provide enablement for a method of determining protein expression by annealing a nucleic acid binding molecule to a nucleic acid transcript encoding the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method of determining protein expression by annealing a nucleic acid binding molecule to a nucleic acid transcript encoding the protein. The specification teaches that it is well known in the art that

overexpression of proteins is usually accompanied by the up-regulation of the production of the corresponding transcripts, thus overexpression of the protein can be shown indirectly by measuring the amount of the corresponding transcripts. This can be done by the use of nucleic acid binding molecules to bind the transcript and nucleic acid binding molecules include DNA heteromers or RNA heteromers (p. 6). One cannot extrapolate the teaching of the specification to the scope of the claims because contrary to Applicant's statement on page 6 of the specification, it is well known in the art that expression levels of proteins are neither necessarily dictated by, nor predictable from, the expression of nucleic acid molecules. For example, For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al

(EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475) teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Thus, predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For the above reasons, one would not believe that it is more likely than not that the invention could function as claimed since a case by case comparison of mRNA/protein level expression would appear to be required to enable the invention as claimed. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

10. If Applicant were able to overcome the rejections above, Claims 21 and 22 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method using a chimeric protein consisting of the variable regions of an antibody to Nup88 inserted into the appropriate framework, does not reasonably provide enablement for a method using a chimeric protein wherein said chimeric protein comprises at least one CDR region of the monoclonal antibody bearing accession number DSM ACC 2457. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to an undefined chimeric protein, a chimeric protein which comprises at least one CDR region of a claimed Mab. This includes a chimeric protein which comprises none, one, two or all three of the CDR regions of either/or both the light or heavy chain of the antibody. The specification teaches that recombinant antibodies such as chimeric proteins that exhibit homology to antibodies of mammals are protein binding molecules and further teaches that a preferred protein binding molecule is a chimeric protein which is characterized in that at least one CDR region of said monoclonal antibody is virtually identical with the corresponding counterpart of 149/1/1 (p. 5). One cannot extrapolate the teaching of the specification to the enablement of the claim because the specification gives no guidance on or exemplification of how to make the claimed chimeric protein so that it will function as claimed. The specification fails to teach the degree of antibody homology required, does not teach how identical the claimed CDR region must be with the corresponding counterpart of 149/1/1 or which virtually identically CDR could be successfully used in the chimeric protein, does not teach what structure, other than an antibody will function as claimed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional

structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding (such as antibody CDR regions) will certainly be among the most conserved (see Bowie et al, Science, 247:1306-1310, 1990, p. 1306, col.2). The specification provides no guidance on structure or residues that are critical to the function of the invention as claimed. Although it is clear that binding specificity of the disclosed antibody is determined by the CDR regions, it is well known that this determination requires the exquisite interaction of the CDRs and the framework region of the antibody. The specification provides no guidance on the interaction of the at least one CDR of the claimed chimeric protein (that is the homolog of antibody) and the rest of the structure of the chimeric protein. Clearly, appropriate framework regions that house the at least one CDR are essential for providing the proper orientation for the at least one CDR to exhibit antigen specificity. Although drawn to humanization techniques, the teaching of Gussow et al (Methods in Enzymology, 1991, 203:99-121) is clearly relevant to the instant rejection. Gussow et al specifically teach that the applicability of antibody humanization techniques relies on, among others, the assumption that the frameworks of the variable domains serve as a scaffold to support the CDRs in a specific way that facilitates antigen binding and further teach that it is of great importance to retain the interactions between the donor CDRs and the acceptor framework as closely as possible to the CDR-framework interactions of the original MAb and further disclose that the affinity of the first fully humanized antibody CAMPATH1 was nearly 40 fold lower compared to the original rat MAb,

apparently because of differences of residues in the framework region of the humanized antibody compared to those of the original antibody, particularly those located close to the CDRs. Clearly, alteration of even one amino acid residue can alter the packing of the residues within the molecule as it was demonstrated that mutation of the human Ser 27 to a Phe (the residue found in the original rat antibody at this position) restored the binding affinity of the humanized antibody close to the original affinity (see page 100). Further, even minor changes in the amino acid sequence of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function (Rudikoff et al, PNAS, USA, 1982, 79: 1979). Rudikoff et al teach that alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein results in the loss of antigen-binding function. Queen et al, PN-5,585,089, teach that the donor CDRs could be distorted, and the affinity of a humanized antibody could be reduced, if the amino acids immediately adjacent to the CDRs are from the acceptor human immunoglobulin (column 14, category 3). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein binding molecule. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

11. Claims 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a whole protein consisting of the amino

acid sequence of Accession number YO8612 for use as a control sample, does not reasonably provide enablement for a part of the sequence/antigenic part for use as a control sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In the interests of compact prosecution, although claims 27-28 are dependent upon indefinite claims 25-26 and Examiner cannot determine what is actually being claimed, the limitations of claims 27-28 drawn to part of the sequence/antigenic part of the amino acid sequence will be addressed here.

The claims are drawn to a part of the sequence/antigenic part for use as a control sample. The specification as originally filed claims an antigen part of Nup88 for control reactions (see claim 11) and teaches that preferably, the diagnostic kit contains an antigenic part of Nup88 for control reactions (p. 6, lines 15-16). One cannot extrapolate the teaching of the specification to scope of the claims because the specification provides neither guidance on nor exemplification of any part/antigenic part of the protein that will function as claimed as a control sample. For example, Roitt et al, 1998, Immunology, 4th ed, Mosby, London teach that although it is possible to produce antibodies (protein binding molecules) to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). This is exemplified by the

teaching of Holmes (Exp. Opin. Invest. Drugs, 2001, 10(3):511-519) who teaches that rabbits were immunized with synthetic peptides which in each case generated high anti-peptide specific immunoreactivities, however, none of the antibodies exhibited binding to the full length antigen. The author concludes that 'Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability (p. 513, col 1). The specification provides no guidance drawn to the issue of which "part" of the protein should be used as a control since it is clear that although most "parts" of a protein are antigenic, it is also true that protein binding molecules that bind to the complete antigen won't bind to many of these parts. In the absence of guidance from the specification, it cannot be determined which "part" would function as claimed. Furthermore, the use of the "part" does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in the binding of a protein binding molecule. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quarterary structure of a protein in a physiological situation. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art to determine which "parts" would function as claimed. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

12. Claims 13-28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-28 are indefinite because they recite a Genebank accession number and the sequences corresponding to Genebank accession numbers can be modified, changed, and/or updated. Thus the cited sequence may vary or change over time.

Claims 21-22 are indefinite because claim 21 recites the term "chimeric". The exact meaning of the word chimeric is not known and the term is not defined by the specification. The term chimeric is generic to a class of antibodies which are products of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies.

Claim 23 is indefinite because there is no antecedent basis for the claimed protein binding molecule in claim 13 from which claim 23 depends.

Claims 25-28 are indefinite because there is no antecedent basis for the claimed kit in claim 21 from which claim 25 depends or in claim 22 from which claim 26 depends.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 24 is rejected under 35 U.S.C. § 102(b) as being anticipated by Boehringer Mannheim Biochemicals, 1994 Catalog, p. 93.

Claim 24 recites a diagnostic kit for carrying out a method. However the only material or reagent claimed in the kit is a nucleic acid that anneals to a nucleic acid transcript that encodes the protein consisting of the amino acid sequence of Accession number YO8612. For the purposes of examination, the limitation of a "diagnostic kit" is viewed as a recitation of intended use and therefore is not given weight in comparing the claim with the prior art. Claim 24 reads on the ingredient *per se*, which is a nucleic acid that anneals to a nucleic acid transcript that encodes the protein consisting of the amino acid sequence of Accession number YO8612.

The Boehringer Mannheim catalog teaches a kit comprising random primers that encompass all possible 6-nucleotide sequences (see page 93, Catalog No. 1034 731/1006 924) a subset of which will anneal to every nucleic acid transcript. All of the limitations of the claims are met.

15. Claim 12 is free of the art and allowable.

16. All other objections and rejections recited in Paper No. 7 are withdrawn.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Stephen Rawlings, PhD
June 27, 2002

SUSAN UNGAR, PH.D
PRIMARY EXAMINER